Suppression of ventricular extrasystoles by perhexiline[1]

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SUMMARY   The antiarrhythmic effects of perhexiline were investigated in 13 of 20 patients with frequent and long standing ventricular extrasystoles in a double blind crossover trial using 24-hour electrocardiograph tape recordings, routine electrocardiograms, and treadmill exercise testing. With a dose of 300 to 400 mg per day, there was a significant decrease (mean 41%) in the number of ventricular extrasystoles per 24 hours. There were large differences in the individual responses to perhexiline, which were significantly related to the diurnal variations of ventricular extrasystoles: those patients whose ventricular extrasystoles disappeared spontaneously during sleep were less likely to respond to perhexiline than those whose ventricular extrasystoles persisted throughout the night. Suppression of ventricular extrasystoles was also apparent from the routine electrocardiogram and the exercise tests. Side effects (dizziness and unsteadiness) were troublesome in 5 of 20 patients. It is concluded that in selected patients perhexiline is an effective antiarrhythmic drug, and is likely to be most useful in patients with coexisting angina and ventricular extrasystoles. Because of its potential toxicity, it should not be used as a drug of first choice.

Perhexiline is an antianginal drug which is neither a beta-blocker nor a primary vasodilator (Hudak et al., 1973). It increases myocardial blood flow in animals (Klassen et al., 1976), and in man may improve left ventricular function and myocardial oxygen extraction (Rowe et al., 1970); during exercise the tachycardia is reduced, and exercise tolerance improved in patients with angina (Cherchi et al., 1973). It also reduces automaticity and depresses impulse conduction in ventricular muscle (Ten Eick and Singer, 1973), and there is some evidence that it may have antiarrhythmic properties in man (Drake et al., 1973; Sukerman, 1973). We report here a clinical trial of its efficacy as an antiarrhythmic drug in patients with frequent ventricular extrasystoles.

Patients and methods

Twenty patients known to have frequent and long standing ventricular extrasystoles judged on clinical ground to need treating were included in the trial. Patients were excluded if they had had a myocardial infarction within 3 months, atrioventricular con-

duction defect, atrial fibrillation, were on beta-blocking drugs, or any antiarrhythmic drug other than digoxin. Of the 20 patients, 14 had ischaemic heart disease, 3 were on digoxin, and 1 was a diabetic requiring insulin. The average age was 57 years, and 16 were men.

Each patient acted as his own control, and was seen at 2-weekly intervals. For the first period of 2 weeks the patient received no drug, followed by 2 weeks of placebo. After this the patients were randomised to receive either 4 weeks of placebo followed by 4 weeks of perhexiline (200 mg b.d.), or vice versa. For the final 2 weeks the patient received no drugs. There were thus 7 periods of 2 weeks altogether. At the end of each period a clinical examination, 12-lead electrocardiogram, and 24-hour electrocardiograph tape recording were carried out. In addition, a treadmill exercise test, using the Bruce procedure, was made at the end of periods 2 (placebo), 4 (placebo/perhexiline), and 6 (perhexiline/placebo). Blood for liver function tests was also taken at these times. Patient compliance was assessed by counting pills at the end of each period.

The tape recordings were made on an Oxford Medilog recorder, using praecordial electrocardiograph leads in the V5 position. Tapes were analysed at 25 times the recording speed by a semiautomatic method described previously (Goulding and Cobern, 1976). Each QRS complex was detected by an

analogue processor and classified as premature or not according to the coupling interval.

A variable portion of the QRS complex was gated and fed into two filters, one low pass and one high pass. The output from the filters varied according to the frequency content of the QRS complex; ventricular extrasystoles were detected by a combination of prematurity and low frequency content. Counts were made for the total number of heart beats and ventricular extrasystoles over consecutive periods of one hour. Diurnal variations of ventricular extrasystoles were assessed by comparing the frequency of ventricular extrasystoles during the night (1 to 4 am) with the daytime frequency (9 am to 9 pm).

The 12-lead electrocardiograms taken at each visit were also analysed for the frequency of ventricular extrasystoles. For the treadmill tests 3 minutes of resting electrocardiogram were taken followed by 3 minutes at each work load. The end-point of exercise was taken according to the usual clinical criteria (American Heart Association, 1972) during the first test. Subsequent tests were carried out for the same length of time, so that it was not possible to assess changes in exercise tolerance.

The results were analysed for the effects of the drug on ventricular extrasystoles only if there was no spontaneous decrease during the trial period. Five patients were withdrawn during the early stages of the trial, 4 because the second and subsequent tape recordings showed a distinct decrease of ventricular extrasystoles (to less than 1000 per 24 hours), and 1 because of side effects during the placebo period. One other patient was later withdrawn because of side effects during the perhexiline period. In 1 patient the extrasystoles were thought to be supraventricular with aberrant conduction, and the results of this patient were analysed separately. It was thus possible to assess the effects of perhexiline on ventricular extrasystoles in 13 patients. Because there was considerable variability in the number of ventricular extrasystoles per 24 hours from one recording to the next, the average counts on no drug and placebo were combined for comparison with perhexiline.

Results are expressed as mean ± standard deviation. Statistical comparison between groups were made by t tests.

Results

Fig. 1 shows the experimental design and the overall results for one patient who responded favourably to perhexiline. For the group as a whole there was no consistent placebo effect, and the
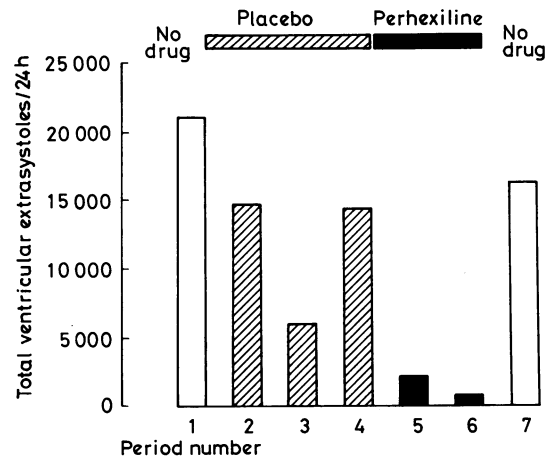

Fig. 1   *Successive 24-hour counts of ventricular extrasystoles in a patient who responded favourably to perhexiline. Open bars = no drug; hatched = placebo; solid = perhexiline. Each period was of 2 weeks.*

average number of ventricular extrasystoles per 24 hours decreased from 11 424 ± 7100 on no drug and placebo to 6020 ± 4904 on perhexiline, a significant decrease ($P < 0.01$) of 41 per cent. There was a very wide range of response, however, ranging from the 89 per cent suppression shown by the patient in Fig. 1 to no change or a small increase on perhexiline. Eight of 13 patients showed a decrease of more than 50 per cent, and 4 a decrease of less than 10 per cent. The difference between the responders and non-responders could not be attributed to differences in patient compliance, to any feature of the ventricular extrasystoles detectable on the 12-lead electrocardiogram, or to the associated clinical diagnosis. We have noted previously (Pickering *et al.*, 1976) that patients vary greatly in the extent to which ventricular extrasystoles are suppressed during sleep (assessed by comparing the frequency of ventricular extrasystoles during the night and during the day, as described above), some showing little or no change, others complete suppression. Three of the present series of patients had complete absence of ventricular extrasystoles during sleep despite multifocal and paired extrasystoles in 2 of them while awake. None of these 3 showed any therapeutic response to perhexiline, and for all 13 patients there was a significant negative correlation ($r = 0.65$, $P < 0.02$) between the degree to which extrasystoles were suppressed during sleep while on no treatment, and their suppression by perhexiline (Fig. 2).

Comparison of the mean 24-hour heart rates on no drug and placebo versus perhexiline showed no
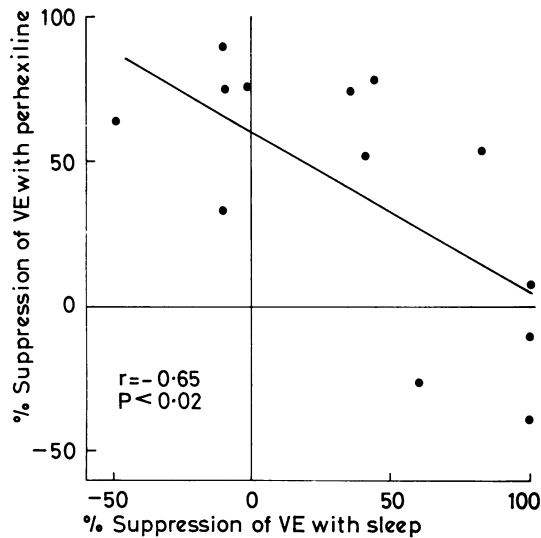
Fig. 2 *Relation between spontaneous suppression of ventricular extrasystoles during sleep and suppression produced by perhexiline. Those patients whose ventricular extrasystoles disappeared during sleep responded less well to the drug.*

significant difference (the mean rates were 75·4 ± 8·2 and 72·3 ± 5·7 per min, respectively). The responders and non-responders could not be distinguished by any effect of the drug on heart rate.

In everyday clinical practice it is often necessary to attempt to assess the response to antiarrhythmic drugs from the patient's symptoms and from the routine electrocardiogram. We, therefore, also examined the routine electrocardiograms to see to what extent the therapeutic response could be assessed from them. There was a significant correlation between the frequency of ventricular extrasystoles on the routine electrocardiograms and on the corresponding 24-hour tapes (r = 0·61, P < 0·001), but the predictive value of a single electrocardiogram was poor. There was also a

significant correlation (r = 0·77, P < 0·01) between the degree of suppression of ventricular extrasystoles produced by perhexiline when estimated from the routine electrocardiograms and from the 24-hour tapes.

The effects of perhexiline were also assessed from the exercise tests. There was no significant effect of the drug on the resting heart rate (87 ± 19 per min on placebo, and 83 ± 18 on perhexiline), but the rates during the last 3 minutes of exercise were lower (130 ± 18 per min on placebo and 122 ± 24 on perhexiline; P < 0·05). Ventricular extrasystoles were significantly reduced by perhexiline both at rest and during exercise (by 64% and 96%, respectively; P < 0·05 for each). The most dramatic effects of perhexiline were seen in the patient whose tracings are shown in Fig. 3. When untreated he had repeated salvoes of multiple ventricular extrasystoles during exercise and during the recovery period, which were almost wholly abolished by perhexiline.

Side effects were reported by 3 out of 20 patients while on placebo (dizziness in 2 ,lightheadedness in 1), and in 5 of 20 while on perhexiline; these consisted of dizziness and unsteadiness in 4, and depression and weakness in 1. In 2 of them the symptoms were greatly improved by reducing the dose of perhexiline to 300 mg daily, but 2 found the drug unacceptable. Two patients showed impairment of liver function tests during the perhexiline period, characterised by a rise in AST, LDH, and alkaline phosphatase. The diabetic patient who needed insulin did not have any apparent change in his diabetic control while on perhexiline.

Discussion

The decision to treat patients with ventricular extrasystoles is a difficult one to make, particularly because the extrasystoles often cause no symptoms. Two factors that are associated with an increased

Untreated

Perhexiline

Fig. 3 *Multiple ventricular extrasystoles occurred during the recovery period after exercise in this patient (upper trace), which were completely suppressed by perhexiline (lower trace).*

risk of sudden death are a high frequency of extra-systoles (Hinkle *et al.*, 1969) and the presence of coronary artery disease (Chiang *et al.*, 1969). A drug that is effective both against angina and against ventricular extrasystoles is thus particularly useful, since the majority of patients on long term treatment for extrasystoles are likely to have coronary disease. Our results are in general agreement with two earlier reports (Drake *et al.*, 1973; Sukerman, 1973) that perhexiline does have a significant anti-arrhythmic action, though not in all patients. This effect can be explained by the known electro-physiological effects of the drug, in which respect it resembles procainamide and quinidine (Ten Eick and Singer, 1973). Like lignocaine, it has little effect on atrial muscle (Ten Eick and Singer, 1973), which is consistent with our finding of no anti-arrhythmic effect in a patient with supraventricular extrasystoles. One problem which this type of clinical trial cannot answer is what constitutes a therapeutic response? The ultimate answer to this must be the prevention of sudden death, but this can be shown only by large scale and long term studies, such as are now being carried out for beta-blocking drugs (Multicentre International Study, 1975). In the meantime our best index must be the overall suppression of ventricular extrasystoles, and in this respect perhexiline compares favourably with other oral antiarrhythmic drugs (Jelinek *et al.*, 1974; Campbell *et al.*, 1975; Niarchos, 1976).

No antiarrhythmic drug is effective in all patients, and it would be of great help to be able to predict which patients are likely to respond and which are not. Though the numbers are small, our results suggest that the diurnal rhythm of ventricular extrasystoles could be useful in this respect, since patients whose ventricular extrasystoles disappeared spontaneously during sleep did not show any response to the drug. The reason for the dis-appearance of ventricular extrasystoles during sleep is not known, though we have obtained evidence that bradycardia may be the single most important factor (Pickering *et al.*, 1977).

While 24-hour electrocardiographic monitoring must remain the yardstick by which antiarrhythmic therapy is judged, our results also suggest that a reasonable idea of the therapeutic response can be obtained by doing repeated electrocardiographic recordings, provided of course that the patient has a high frequency of ventricular extrasystoles in the first place. Exercise testing also provided evidence for the suppression of extrasystoles by perhexiline, and it is of interest that this effect appeared to be even greater during exercise than at rest. Exercise-induced ventricular extrasystoles are more likely to be associated with coronary disease, and probably carry a more sinister prognosis (Vedin *et al.*, 1972).

As with many other antiarrhythmic drugs, there appears to be a relatively narrow range between the therapeutic and the toxic dose of perhexiline. We found the central nervous system side effects to be the most troublesome, but these could often be alleviated by reducing the dose. The abnormalities of liver function tests have been previously noted (Pilcher *et al.*, 1973), but have not been found to constitute a major problem (Howard and Russell Rees, 1976). The most serious side effect which has been reported is peripheral neuropathy (Bourrat *et al.*, 1975; L'Hermitte *et al.*, 1976). Though none of the present series of patients developed this, we have encountered one patient whose angina res-ponded to perhexiline better than to beta-blockade, but who developed neuropathy while on perhexiline.

In conclusion, perhexiline does cause a signifi-cant suppression of ventricular extrasystoles, but its effectiveness is limited by a lack of response in some patients, and by side effects in others. Because of its potent antianginal properties, it is likely to prove most useful in patients with coronary artery disease who have both angina and ventricular extrasystoles, but at the present time we recommend that it be reserved for patients with life-threatening arrhythmias or angina which does not respond to beta-blockers.

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